Acthar Speaker Training

H.P. Acthar® GEL
(repository corticotropin injection) 80 U/mL

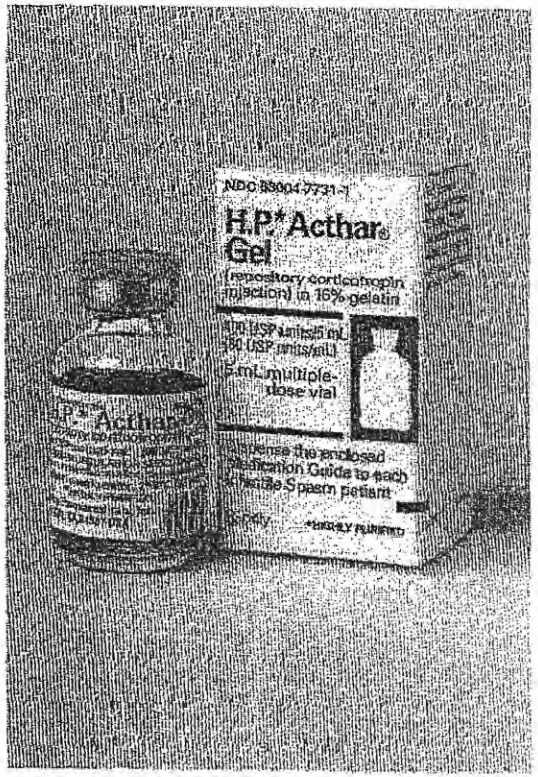
The History of ACTH and Actharin in the Treatment of MS

- Prior to 1960, most clinical trials in MS were poorly controlled and generally not informative
- ACTH had the first placebo-controlled study of MS relapses in 1961. The trial demonstrated more rapid improvement in the ACTH group compared to placebo[1]
- The National Cooperative Trial of ACTH in acute relapses of MS in 1965 served as the model for future medication trials in MS[2,3]

1. Miller H et al. *Lancet.* 1961;2:1120-1122.
2. Rose AS et al. *Neurology.* 1968;18(Suppl):1-10.
3. Rose AS et al. *Neurology.* 1970;20:1-59.

Acthar Product Information

- A preparation of ACTH in 16% gelatin
  - The gelatin allows the drug to be released slowly over a long period of time, extending the duration of activity
  - Prolonged release after intramuscular (IM) or subcutaneous (SC) injection
- ACTH is a 39 amino acid peptide
- Available as a 5-mL multidose vial containing 80 U/mL (400 U/vial)
- Can be administered by self-injection



Refer to the full prescribing information for H.P. Acthar Gel for a complete list of adverse events (AEs), precautions, and warnings.

H.P. Acthar Gel [package insert]. Questcor Pharmaceuticals, Inc.

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Acthar Indications

- Acthar is approved for the treatment of acute relapses of MS in adults
  - Acthar is effective in accelerating the resolution of acute relapses
  - There is no evidence that Acthar affects the overall outcome or progression of the disease
  - H.P. Acthar® Gel (repository corticotropin injection) is an adrenocorticotropic hormone (ACTH) analogue used for:
    - Monotherapy treatment of infantile spasms (IS) in infants and children under 2 years of age.
    - The treatment of exacerbations of multiple sclerosis in adults.
    - For inducing a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus.
    - The following: rheumatic disorders; collagen diseases; dermatologic diseases; allergic states; ophthalmic diseases and respiratory diseases.
- Acthar is approved for the treatment of optic neuritis

Refer to the full prescribing information for H.P. Acthar Gel for a complete list of indications.

H.P. Acthar Gel [package insert]. Questcor Pharmaceuticals, Inc.

Common adverse reactions for H.P. Acthar Gel are similar to those of corticosteroids and include, fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain.

Acthar Dosing in MS

Treatment of Acute Relapses of MS

- Daily IM or SC doses of 80-120 U may be administered for 2-3 weeks
- Dosage should be individualized according to the medical condition of each patient
- Dosing frequency should be determined according to the severity of the disease and the initial response of the patient
- It may be necessary to taper the dose

Refer to the full prescribing information for H.P. Acthar Gel for a complete list of adverse events (AEs), precautions, and warnings.

H.P. Acthar Gel [package insert]. Questcor Pharmaceuticals, Inc.

Important Safety Information

Acthar should never be given intravenously. It is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency or adrenocortical hyperfunction or sensitivity to proteins of porcine origin. Acthar is contraindicated in children under 2 years of age with suspected congenital infections. Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar.

The adverse effects that may occur with Acthar are related primarily to its steroidogenic effects and are similar to corticosteroids. There may be increased susceptibility to new infection and increased risk of reactivation of latent infections. Adrenal insufficiency may occur after abrupt withdrawal of the drug following prolonged therapy. Cushing's syndrome, elevated blood pressure, salt and water retention, and hypokalemia may be seen. Masking of symptoms of other underlying disease/disorders may occur. There is a risk of gastrointestinal perforation and bleeding with increased risk of perforation in patients with certain GI disorders. Onset or worsening of euphoria, insomnia, irritability (especially in infants), mood swings, personality changes, depression, and psychosis may occur.

Important Safety Information

Caution should be used when prescribing Acthar to patients with diabetes or myasthenia gravis. Prolonged use may produce cataracts, ocular infections or glaucoma. Use in patients with hypothyroidism or liver cirrhosis may result in an enhanced effect. There may be negative effects on growth and physical development and decreases in bone density.

Specific adverse reactions reported in infantile spasms (IS) clinical trials in infants and children under 2 years of age included: infection, hypertension, irritability, Cushingoid symptoms, constipation, diarrhea, vomiting, pyrexia, weight gain, increased appetite, decreased appetite, nasal congestion, acne, rash, and cardiac hypertrophy. Convulsions were also reported, but these may actually be occurring because some IS patients progress to other forms of seizures and IS sometimes mask other seizures, which become visible once the clinical spasms from IS resolve. Other adverse reactions in adults and children over 2 years of age included: abdominal distension, anxiety, asthma, chest discomfort, congestive heart failure, dizziness, dyspnea, erythema, fatigue, flushing, headache, hyperhidrosis, hypersensitivity or allergic reactions, injection site pain, muscle weakness, palpitations, peripheral edema, tachycardia, and weakness.

This is a summary only. For a complete list of indications, contraindications, warnings, precautions, and potential adverse reactions associated with H.P. Acthar Gel, please refer to the full Prescribing Information.

Studies of ACTH in MS Relapse

- In 2 randomized, placebo controlled studies, ACTH was shown to be effective in relieving symptoms in patients who had an MS relapse[1,2]
- In 3 comparative trials, there was no significant difference between ACTH and steroids[3-5]

1. Miller H, et al. *Lancet*. 1961;2:1120-1122.
2. Rose AS, et al. *Neurology*. 1970;20:1-59.
3. Barnes MP, et al. *J Neurol Neurosurg Psychiatry*. 1985;48:157-159.
4. Thompson AJ, et al. *Neurology*. 1989;39(7):969-971.
5. Milanese C, et al. *Eur Neurol*. 1989;29:10-14.

Acthar Efficacy in Other Indications Demonstrates Mechanisms That Are Distinct From Exogenous Corticosteroids

Infantile Spasms

- Acthar Efficacy: > 86%; Corticosteroid Efficacy: < 30%[1]

Proteinuria in Nephrotic Syndrome

- Acthar showed efficacy in patients with idiopathic types of nephropathy including idiopathic membranous nephropathy, focal segmental glomerulosclerosis, and IgA nephropathy*

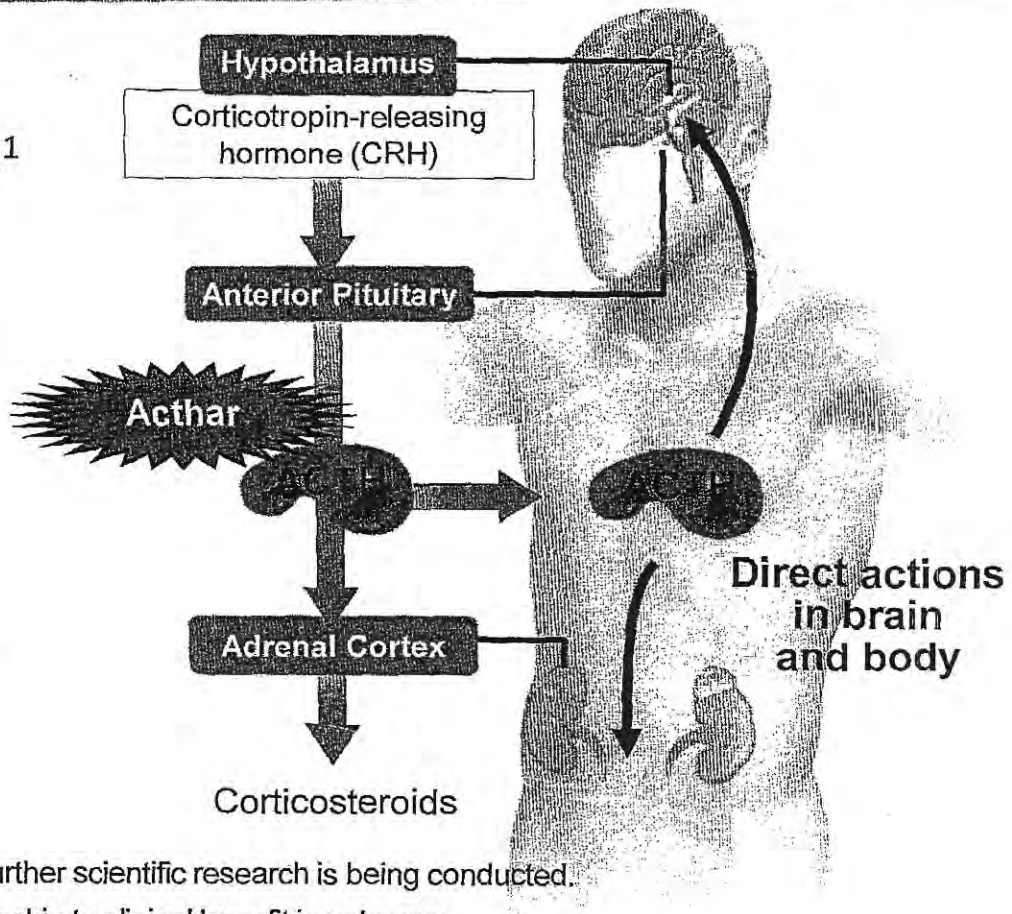
**These results are based on a retrospective evaluation of clinical experience and may not be fully representative of outcomes in the overall patient population.*

FSGS = Focal segmental glomerulosclerosis.

1. H.P. Acthar Gel [package insert]. Questcor Pharmaceuticals, Inc.
2. Bomback et al. *Drug Des Devel Ther.* 2011;5:147-53.

ACTH May Have Broad Immunomodulatory Properties

- Acthar's primary component is the melanocortin peptide ACTH.[1] ACTH may have inflammation and immune properties[2]
  - Induces natural corticosteroid hormones[1]
    - Cortisol
    - Aldosterone
    - Other hormones
  - Anti-inflammatory properties through melanocortin receptor activation[2]



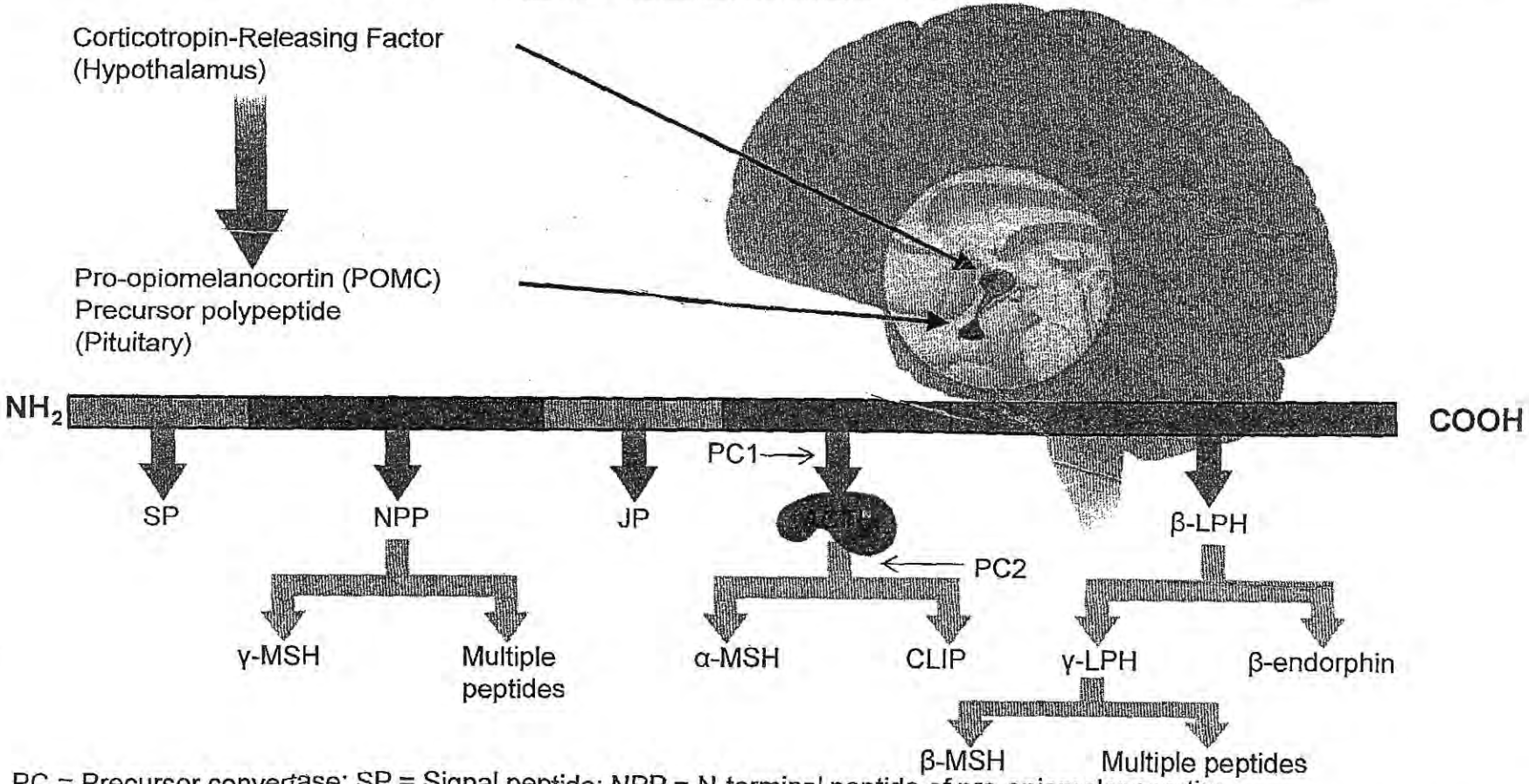
While the exact mechanism of action of Acthar is unknown, further scientific research is being conducted.

This information is based on non-clinical data and the relationship to clinical benefit is unknown.

Refer to the full prescribing information for H.P. Acthar Gel for a complete list of AEs, precautions, and warnings.

1. H.P. Acthar Gel [package insert]. Questcor Pharmaceuticals, Inc; 2. Catania A. *J Leukoc Biol.* 2007;81:383-92.

ACTH is a Melanocortin Peptide



PC = Precursor convertase; SP = Signal peptide; NPP = N-terminal peptide of pro-opiomelanocortin; JP = Joining peptide; ACTH = Adrenocorticotropic hormone; LPH = Lipotropin hormone; MSH = Melanocyte stimulating hormone; CLIP = Corticotropin-like intermediate peptide

Catania et al. *J Leukoc Biol*. 2007;81:383-392.

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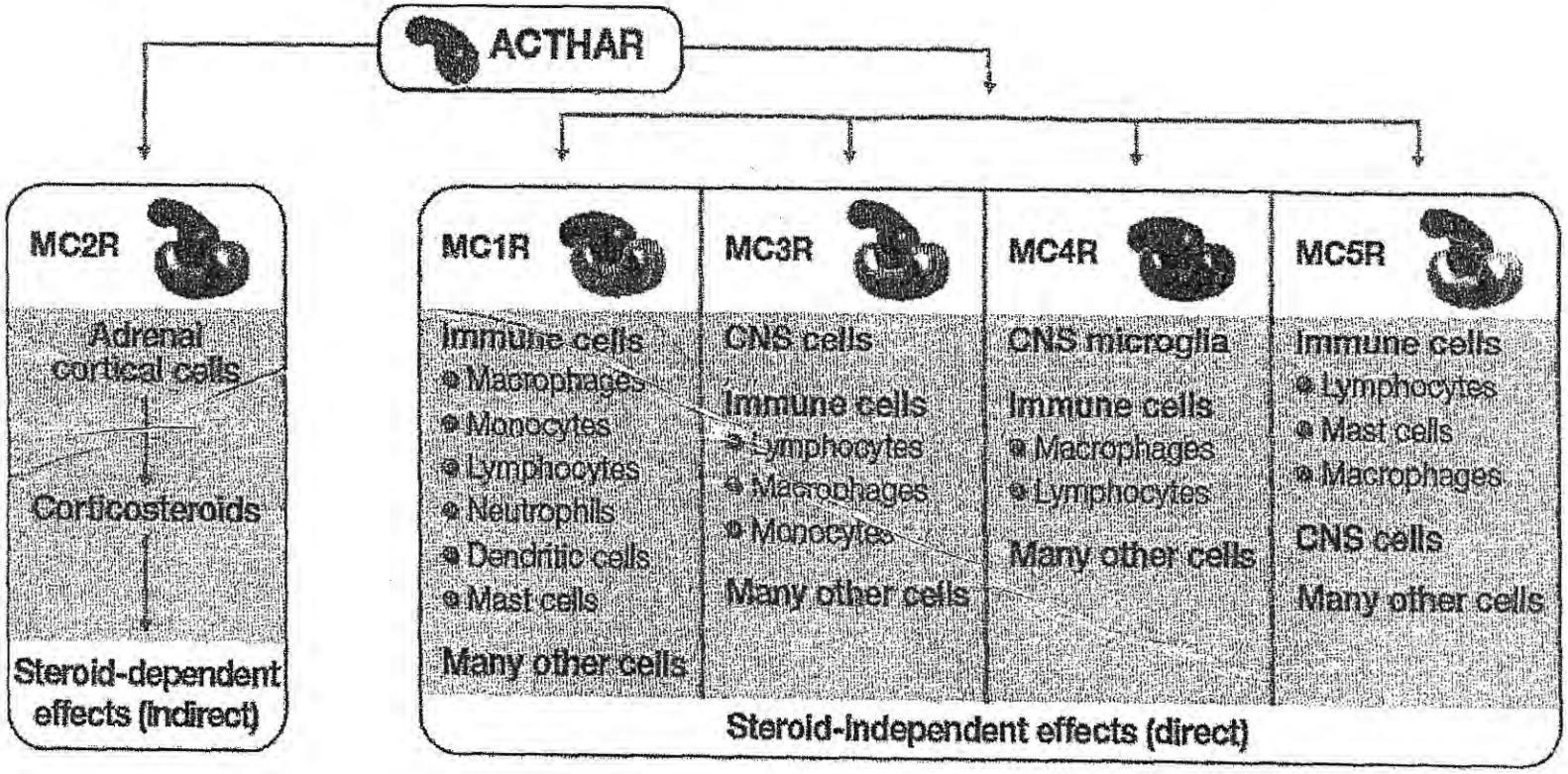
Acthar and Melanocortin Peptides Function Through Melanocortin Receptors (MCRs)



While the exact mechanism of action of Acthar is unknown, further investigation is being conducted. This information is based on nonclinical data and the relationship to clinical benefit is unknown.

Data on file. RD-010-00; RD-011-00; Catania A, et al. *Pharmacol Rev.* 2004;56:1-29.

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Melanocortin Summary

- Melanocortin peptides are derived from the common precursor pro-opiomelanocortin (POMC) and include α-, β-, γ-MSH and ACTH
- Five receptor subtypes for melanocortins (MC1–MC5) are widely distributed in brain regions and in peripheral cells
- Melanocortin receptor activation by ligands has marked anti-inflammatory and immunomodulatory properties
- Steroid-dependent immunomodulatory properties of Acthar occur through activation of MC2R in the adrenal cortex and secretion of endogenous corticosteroids
- Acthar and other melanocortins can bind to MC1R, MC3R, MC4R, and MC5R, which may have a direct immunomodulatory properties

This information is based on nonclinical data and the relationship to clinical benefit is unknown.
While the exact mechanism of action of Acthar is unknown, further investigation is being conducted.

Take Control of Your MS Relapses

Know Your Treatment Options

PM-521-03 1/18

H.P. Acthar GEL
(repository corticotropin injection) 80 U/mL

Key Content Updates

More patient-friendly formatting and language

More streamlined information regarding MS relapses

A new optic neuritis simulation slide

A more robust discussion of MS relapse management

A new slide outlining MS resources

New optional modules:

- What causes a relapse?
- How is Acthar given?
- How can you take an active role in relapse management?

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use H.P. Acthar Gel safely and effectively. See full prescribing information for H.P. Acthar Gel.

H.P. Acthar Gel (repository corticotropin injection) INJECTION, GEL for INTRAMUSCULAR | SUBCUTANEOUS use

Initial U.S. Approval: 1952

RECENT MAJOR CHANGES

- Indications and Usage, (1) 10/10
- Dosage and Administration, (2) 10/10
- Contraindications, Infantile Spasms (4) 10/10
- Warnings and Precautions (5) 10/10

INDICATIONS AND USAGE

- H.P. Acthar Gel is an adrenocorticotropic hormone (ACTH) analogue indicated as monotherapy for the treatment of infantile spasms in infants and children under 2 years of age. (1.1)
- H.P. Acthar Gel is indicated for the treatment of exacerbations of multiple sclerosis in adults. (1.2)
- H.P. Acthar Gel may be used for the following disorders and diseases: rheumatic; collagen; dermatologic; allergic states; ophthalmic; respiratory; and edematous state. (1.3 to 1.9)

DOSAGE AND ADMINISTRATION

- In the treatment of infantile spasms, the recommended dose is 150 U/m² divided into twice daily intramuscular injections of 75 U/m². After 2 weeks of treatment, dosing should be gradually tapered and discontinued over a 2-week period. (2.1)
- In the treatment of acute exacerbations of multiple sclerosis, daily intramuscular or subcutaneous doses of 80-120 units for 2-3 weeks may be administered. It may be necessary to taper the dose. (2.2)
- In the treatment of other disorders and diseases, dosing will need to be individualized depending on the disease under treatment and the medical condition of the patient. It may be necessary to taper the dose. (2.3)

DOSAGE FORMS AND STRENGTHS

- 5 mL multi-dose vial containing 80 USP units per mL (3)

CONTRAINDICATIONS

- H.P. Acthar Gel should never be given intravenously.
- H.P. Acthar Gel is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, or sensitivity to proteins of porcine origin.
- Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of H.P. Acthar Gel.
- H.P. Acthar Gel is contraindicated in children under 2 years of age with suspected congenital infections. (4)
- Treatment of conditions listed within the INDICATIONS section is contraindicated when they are accompanied by primary adrenocortical insufficiency or adrenocortical hyperfunction. (4)

WARNINGS AND PRECAUTIONS

- Infections: Increased susceptibility to new infection and increased risk of exacerbation, dissem nation or reactivation of latent infections. Signs and symptoms of infection may be masked. (5.
- Adrenal Insufficiency after Prolonged Therapy: Monitor for effects of hypothalamic-pituitary-ax suppression after stopping treatment. (5.2)
- Cushing's Syndrome: May occur after prolonged therapy. Monitor for signs and symptoms. (5.
- Elevated Blood Pressure, Salt and Water Retention and Hypokalemia: Monitor blood pressure ar sodium and potassium levels. (5.3)
- Vaccination: Do not administer live or attenuated vaccines to patients on immunosuppressi doses. (5.4)
- Masking of Symptoms of Other Underlying Disease/Disorders. Monitor patients for signs of oth underlying disease/disorders that may be masked. (5.5)
- Gastrointestinal Perforation and Bleeding: There is a risk for gastric ulcers and bleeding. There an increased risk of perforation in patients with certain GI disorders. Signs and symptoms may b masked. Monitor for signs of perforation and bleeding. (5.6)
- Behavioral and Mood Disturbances: May include euphoria, insomnia, mood swings, personali changes, severe depression and psychosis. Existing conditions may be aggravated. (5.7)
- Comorbid Diseases: Symptoms of diabetes and myasthenia gravis may be worsened wi treatment. (5.8)
- Ophthalmic Effects: Monitor for cataracts, infections and glaucoma. (5.9)
- Immunogenicity Potential: Neutralizing antibodies with chronic administration may lead to a los of endogenous ACTH activity. (5.10)
- Use in Patients with Hypothyroidism or Liver Cirrhosis: May result in an enhanced effect. (5.11
- Negative Effects on Growth and Physical Development: Monitor pediatric patients on long ter therapy. (5.12)
- Decrease in Bone Density: Monitor for osteoporosis in patients on long term therapy. (5.13)
- Use in Pregnancy: Embryocidal effect. Apprise women of potential harm to the fetus. (5.14)

ADVERSE REACTIONS

- Common adverse reactions for H.P. Acthar Gel are similar to those of corticosteroids and inclu fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and moo changes, increased appetite and weight gain. (6)
- Specific adverse reactions resulting from drug use in children under 2 years of age are increase risk of infections, hypertension, irritability, Cushingoid symptoms, cardiac hypertrophy ar weight gain. (6.1.1)

To report SUSPECTED ADVERSE REACTIONS, contact Questcor Pharmaceuticals, Inc. (800) 411-3065 or (510) 400-0700 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- H.P. Acthar Gel may accentuate the electrolyte loss associated with diuretic therapy. (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: H.P. Acthar Gel has been shown to have an embryocidal effect and should be use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- Pediatric Use: Prolonged use of H.P. Acthar Gel in children may inhibit skeletal growth. If use necessary, it should be given intermittently with careful observation. (5.12 and 8.3)

See 17 for Patient Counseling Information and FDA-approved Medication Guide

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Infantile spasms:

H.P. Acthar Gel (repository corticotropin injection) is indicated as monotherapy for the treatment of infantile spasms in infants and children under 2 years of age.

1.2 Multiple Sclerosis:

H.P. Acthar Gel (repository corticotropin injection) is indicated for the treatment of acute exacerbations of multiple sclerosis in adults. Controlled clinical trials have shown H.P. Acthar Gel to be effective in speeding the resolution of acute exacerbations of multiple sclerosis. However, there is no evidence that it affects the ultimate outcome or natural history of the disease.

1.3 Rheumatic Disorders:

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: Psoriatic arthritis, Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy), Ankylosing spondylitis.

1.4 Collagen Diseases:

During an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis).

1.5 Dermatologic Diseases:

Severe erythema multiforme, Stevens-Johnson syndrome.

1.6 Allergic States:

Serum sickness.

1.7 Ophthalmic Diseases:

Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation.

1.8 Respiratory Diseases:

Symptomatic sarcoidosis.

1.9 Edematous State:

To induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus.

2 DOSAGE AND ADMINISTRATION

2.1 Specific Recommended Dosage Regimen for Infantile Spasms in Infants and Children Under 2 Years of Age

In the treatment of infantile spasms, H.P. Acthar Gel must be administered intramuscularly. The recommended regimen is a daily dose of 150 U/m² (divided into twice daily intramuscular injections of 75 U/m²) administered over a 2-week period. Dosing with H.P. Acthar Gel should then be gradually tapered over a 2-week period to avoid adrenal insufficiency. The following is one suggested tapering schedule: 30 U/m² in the morning for 3 days; 15 U/m² in the morning for 3 days; 10 U/m² in the morning for 3 days; and 10 U/m² every other morning for 6-days.

H.P. Acthar Gel is typically dosed based on body surface area (BSA). For calculation of body surface area, use the following formula

$$BSA(m^2) = \sqrt{\frac{weight\ (\text{kg}) \times height\ (\text{cm})}{3600}}$$

2.2 Recommended Dosage Regimen for the Treatment of Acute Exacerbations in Adults with Multiple Sclerosis

The recommended dose is daily intramuscular or subcutaneous doses of 80-120 units for 2-3 weeks for acute exacerbations.

Dosage should be individualized according to the medical condition of each patient. Frequency and dose of the drug should be determined by considering the severity of the disease and the initial response of the patient.

Although drug dependence does not occur, sudden withdrawal of H.P. Acthar Gel after prolonged use may lead to adrenal insufficiency or recurrent symptoms which make it difficult to stop the treatment. It may be necessary to taper the dose and increase the injection interval to gradually discontinue the medication.

2.3 Recommended Dosage Regimen for Other Indications for Adults and Children Over 2 Years of Age

Dosage should be individualized according to the disease under treatment and the general medical condition of each patient. Frequency and dose of the drug should be determined by considering severity of the disease and the initial response of the patient.

The usual dose of H.P. Acthar Gel is 40-80 units given intramuscularly or subcutaneously every 24-72 hours.

Although drug dependence does not occur, sudden withdrawal of H.P. Acthar Gel after prolonged use may lead to adrenal insufficiency or recurrent symptoms which make it difficult to stop the treatment. It may be necessary to taper the dose and increase the injection interval to gradually discontinue the medication.

2.4 Preparation

H.P. Acthar Gel should be warmed to room temperature before using.

Caution should be taken not to over-pressurize the vial prior to withdrawing the product.

3 DOSAGE FORMS AND STRENGTHS

5 mL multi-dose vial containing 80 USP Units per mL.

4 CONTRAINDICATIONS

H.P. Acthar Gel is contraindicated for intravenous administration.

H.P. Acthar Gel is contraindicated where congenital infections are suspected in infants.

Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of H.P. Acthar Gel.

H.P. Acthar Gel is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction or sensitivity to proteins of porcine origin.

5 WARNINGS AND PRECAUTIONS

The adverse effects of H.P. Acthar Gel are related primarily to its steroidogenic effects. Not all of the adverse events described below have been seen after treatment with H.P. Acthar Gel, but might be expected to occur [*see Adverse Reactions (6.3)*].

5.1 Infections

H.P. Acthar Gel may increase the risks related to infections with any pathogen, including viral, bacterial fungal, protozoan or helminthic infections. Patients with latent tuberculosis or tuberculin reactivity should be observed closely, and if therapy is prolonged, chemoprophylaxis should be instituted.

5.2 Cushing's Syndrome and Adrenal Insufficiency Upon Withdrawal

Treatment with H.P. Acthar Gel can cause hypothalamic-pituitary-axis (HPA) suppression and Cushing's syndrome. These conditions should be monitored especially with chronic use.

Suppression of the HPA may occur following prolonged therapy with the potential for adrenal insufficiency after withdrawal of the medication. Patients should be monitored for signs of insufficiency such as weakness, hyperpigmentation, weight loss, hypotension and abdominal pain.

The symptoms of adrenal insufficiency in infants treated for infantile spasms can be difficult to identify. The symptoms are non-specific and may include anorexia, fatigue, lethargy, weakness, excessive weight loss, hypotension and abdominal pain. It is critical that parents and caregivers be made aware of the possibility of adrenal insufficiency when discontinuing H.P. Acthar Gel and should be instructed to observe for, and be able to recognize, these symptoms [*see Information for Patients (17)*].

The recovery of the adrenal gland may take from days to months so patients should be protected from the stress (e.g. trauma or surgery) by the use of corticosteroids during the period of stress.

The adrenal insufficiency may be minimized in adults and infants by tapering of the dose when discontinuing treatment.

Signs or symptoms of Cushing's syndrome may occur during therapy but generally resolve after therapy is stopped. Patients should be monitored for these signs and symptoms such as deposition of adipose tissue in characteristics sites (e.g., moon face, truncal obesity), cutaneous striae, easy bruisability, decreased bone mineralization, weight gain, muscle weakness, hyperglycemia, and hypertension.

5.3 Elevated Blood Pressure, Salt and Water Retention and Hypokalemia

H.P. Acthar Gel can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium and calcium. Dietary salt restriction and potassium supplementation may be necessary. Caution should be used in the treatment of patients with hypertension, congestive heart failure, or renal insufficiency.

5.4 Vaccination

Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of H.P. Acthar Gel. Killed or inactivated vaccines may be administered; however, the response to such vaccines can not be predicted. Other immunization procedures should be undertaken with caution in patients who are receiving H.P. Acthar Gel, especially when high doses are administered, because of the possible hazards of neurological complications and lack of antibody response.

5.5 Masking Symptoms of Other Diseases

H.P. Acthar Gel often acts by masking symptoms of other diseases/disorders without altering the course of the other disease/disorder. Patients should be monitored carefully during and for a period following discontinuation of therapy for signs of infection, abnormal cardiac function, hypertension, hyperglycemia, change in body weight and fecal blood loss.

5.6 Gastrointestinal Perforation and Bleeding

H.P. Acthar Gel can cause GI bleeding and gastric ulcer. There is also an increased risk for perforation in patients with certain gastrointestinal disorders. Signs of gastrointestinal perforation, such as peritoneal irritation, may be masked by the therapy. Use caution where there is the possibility of impending perforation, abscess or other pyogenic infections, diverticulitis, fresh intestinal anastomoses, and active or latent peptic ulcer.

5.7 Behavioral and Mood Disturbances

Use of H.P. Acthar Gel may be associated with central nervous system effects ranging from euphoria, insomnia, irritability (especially in infants), mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated.

5.8 Comorbid Diseases

Patients with a comorbid disease may have that disease worsened. Caution should be used when prescribing H.P. Acthar Gel in patients with diabetes and myasthenia gravis.

5.9 Ophthalmic Effects

Prolonged use of H.P. Acthar Gel may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves and may enhance the establishment of secondary ocular infections due to fungi and viruses.

5.10 Immunogenicity Potential

H.P. Acthar Gel is immunogenic. Limited available data suggest that a patient may develop antibodies to H.P. Acthar Gel after chronic administration and loss of endogenous ACTH and H.P. Acthar Gel activity. Prolonged administration of H.P. Acthar Gel may increase the risk of hypersensitivity reactions. Sensitivity to porcine protein should be considered before starting therapy and during the course of treatment should symptoms arise.

5.11 Use in Patients with Hypothyroidism or Liver Cirrhosis

There is an enhanced effect in patients with hypothyroidism and in those with cirrhosis of the liver.

5.12 Negative Effects on Growth and Physical Developm

Long-term use of H.P. Acthar Gel may have negative effects on n and physical development in children. Changes in appetite are seen with H.P. Acthar Gel therapy, with the effects becoming more frequent as the dose or treatment period increases. These effects are reversible once H.P. Acthar Gel therapy is stopped. Growth and physical development of pediatric patients on prolonged therapy should be carefully monitored.

5.13 Decrease in Bone Density

Decrease in bone formation and an increase in bone resorption both through an effect on calcium regulation (i.e. decreasing absorption and increasing excretion) and inhibition of osteoblast function may occur. These, together with a decrease in the protein matrix of the bone (secondary to an increase in protein catabolism) and reduced sex hormone production, may lead to inhibition of bone growth in children and adolescents and to the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating therapy, and bone density should be monitored in patients on long term therapy.

5.14 Use in Pregnancy

H.P. Acthar Gel has been shown to have an embryocidal effect. Apprise women of potential harm to the fetus [*see Use in Specific Populations (8.1)*].

6 ADVERSE REACTIONS

Please refer to *Adverse Reactions in Infants and Children Under 2 Years of Age (Section 6.1.1)* for consideration when treating patients with Infantile Spasms. The adverse reactions presented in Section 6.2 are primarily provided for consideration in use in adults and in children over 2 years of age, but these adverse reactions should also be considered when treating infants and children under 2 years of age.

H.P. Acthar Gel causes the release of endogenous cortisol from the adrenal gland. Therefore all the adverse effects known to occur with elevated cortisol may occur with H.P. Acthar Gel administration as well. Common adverse reactions include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain.

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in practice.

6.1.1 Adverse Reactions in Infants and Children Under 2 Years of Age

While the types of adverse reactions seen in infants and children under age 2 treated for infantile spasms are similar to those seen in older patients, their frequency and severity may be different due to the very young age of the infant, the underlying disorder, the duration of therapy and the dosage regimen. Below is a summary of adverse reactions specifically tabulated from source data derived from retrospective chart reviews and clinical trials in children under 2 years of age treated for infantile spasms. The number of patients in controlled trials at the recommended dose was too few to provide meaningful incidence rates or to permit a meaningful comparison to the control groups.

TABLE: Incidence (%) of Treatment Emergent Adverse Events Occurring in ≥2% of H.P. Acthar Gel (repository corticotropin injection) Infants and Children under 2 years of Age

System Organ Class	Recommended 75 U/m² bid n=122, (%)	150 U/m² qd n=37 (%)
Cardiac disorders		
Cardiac Hypertrophy	3	0
Endocrine disorders		
Cushingoid	3	22
Gastrointestinal disorders		
Constipation	0	5
Diarrhea	3	14
Vomiting	3	5
General disorders and administration site conditions		
Irritability	7	19
Pyrexia	5	8
Infections and Infestations		
Infection[1]	20	46
Investigations		
Weight gain	1	3
Metabolism and nutrition disorders		
Increased appetite	0	5
Decreased appetite	3	3
Nervous system disorders		
Convulsion[2]	12	3
Respiratory, thoracic and mediastinal disorders		
Nasal Congestion	1	5
Skin and subcutaneous tissue disorders		
Acne	0	14
Rash	0	8
Vascular disorders		
Hypertension	11	19

[1] Specific infections that occurred at ≥2% were candidiasis, otitis media, pneumonia and upper respiratory tract infections.

[2] In the treatment of Infantile Spasms, other types of seizures/convulsions may occur because some patients with infantile spasms progress to other forms of seizures (for example, Lennox-Gastaut Syndrome). Additionally the spasms sometimes mask other seizures and once the spasms resolve after treatment, the other seizures may become visible.

These adverse reactions may also be seen in adults and children over 2 years of age when treated for other purposes and with different doses and regimens.

6.2 Postmarketing Exp

The following adverse reactio sociated with the use of H.P. Acthar Gel have been identified from postmarketing experience with H.P. Acthar Gel. Only adverse events that are not listed above as adverse events reported from retrospective chart reviews and non-sponsor conducted clinical trials and those not discussed elsewhere in labeling, are listed in this section. Because the adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to use with H.P. Acthar Gel. Events are categorized by system organ class. Unless otherwise noted these adverse events have been reported in infants, children and adults.

6.2.1 Allergic Reactions

Allergic responses have presented as dizziness, nausea and shock (adults only).

6.2.2 Cardiovascular

Necrotizing angiitis (adults only) and congestive heart failure.

6.2.3 Dermatologic

Skin thinning (adults only), facial erythema and increased sweating (adults only).

6.2.4 Endocrine

Decreased carbohydrate tolerance (infants only) and hirsutism.

6.2.5 Gastrointestinal

Pancreatitis (adults only), abdominal distention and ulcerative esophagitis.

6.2.6 Metabolic

Hypokalemic alkalosis (infants only).

6.2.7 Musculoskeletal

Muscle weakness and vertebral compression fractures (infants only).

6.2.8 Neurological

Headache (adults only), vertigo (adults only), subdural hematoma, intracranial hemorrhage (adults only), and reversible brain shrinkage (usually secondary to hypertension) (infants only).

6.3 Possible Additional Steroidogenic Effects

Based on steroidogenic effects of H.P. Acthar Gel certain adverse events may be expected due to the pharmacological effects of corticosteroids. The adverse events that may occur but have not been reported for H.P. Acthar Gel are:

6.3.1 Dermatologic

Impaired wound healing, abscess, petechiae and ecchymoses, and suppression of skin test reactions.

6.3.2 Endocrine

Menstrual irregularities.

6.3.3 Metabolic

Negative nitrogen balance due to protein catabolism.

6.3.4 Musculoskeletal

Loss of muscle mass and aseptic necrosis of femoral and humeral heads.

6.3.5 Neurological

Increased intracranial pressure with papilledema; (pseudo-tumor cerebri) usually after treatment, and subdural effusion.

6.3.6 Ophthalmic

Exophthalmos.

7 DRUG INTERACTIONS

Formal drug-drug interaction studies have not been performed.

H.P. Acthar Gel may accentuate the electrolyte loss associated with diuretic therapy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Class C: H.P. Acthar Gel has been shown to have an embryocidal effect. There are no adequate and well-controlled studies in pregnant women. H.P. Acthar Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from H.P. Acthar Gel, when treating a nursing mother, a decision should be made whether to discontinue nursing or to discontinue the drug, considering the risk and benefit to the mother.

8.4 Pediatric Use

H.P. Acthar Gel is indicated as monotherapy for the treatment of infantile spasms in infants and children less than 2 years of age. Both serious and other adverse reactions in this population are discussed in Warnings and Adverse Reactions in Infants and Children Under 2 Years of Age [*see Sections 5 and 6.1.1*].

The efficacy of H.P. Acthar Gel for the treatment of infantile spasms in infants and children less than 2 years of age was evaluated in a randomized, single blinded (video EEG interpreter blinded) clinical trial and an additional active control supportive trial [*see Clinical Studies (14)*]. A responding patient was defined as having both complete cessation of spasms and elimination of hypsarrhythmia.

Safety in the pediatric population for infantile spasms was evaluated by retrospective chart reviews and data from non-sponsor conducted clinical trials [*see Adverse Reactions (6.1.1)*]. While the types of adverse reactions seen in infants and children under 2 years of age treated for infantile spasms are similar to those seen in older patients, their frequency and severity may be different due to the very young age of the infant, the underlying disorder, the duration of therapy and the dosage regimen. Effects on growth are of particular concern [*see Warnings and Precautions (5.12)*]. Serious adverse reactions observed in adults may also occur in children [*see Warnings and Precautions (5)*].

10 OVERDOSAGE

While chronic exposure to H.P. Acthar Gel at high doses can be associated with a variety of potential serious adverse effects, it is not expected that a single high dose, or even several large doses, has the potential for serious adverse effects compared to a standard dose. There have been no reports of death or acute overdose symptoms from H.P. Acthar Gel in clinical studies or in the published literature.

The intramuscular route of administration makes it unlikely that an inadvertent acute overdose will occur. The typical daily dose of H.P. Acthar Gel to treat an infant that has a BSA of 0.4 m² would be 60 U/day. Using the 1-cc syringe supplied with H.P. Acthar Gel, the maximum amount that can be injected is 80 U/injection, which is a well-tolerated single dose.

11 DESCRIPTION

H.P. Acthar Gel is a highly purified sterile preparation of the adrenocorticotropic hormone in 16% gelatin to provide a prolonged release after intramuscular or subcutaneous injection. Also contains 0.5% phenol, not more than 0.1% cysteine (added), sodium hydroxide and/or acetic acid to adjust pH and water for injection.

ACTH is a 39 amino acid peptide with the following chemical formula:

H-	Ser-	Tyr-	Ser-	Met-	Glu-	His-	Phe-	Arg-	Trp-	Gly-
	1	2	3	4	5	6	7	8	9	10
	Lys-	Pro-	Val-	Gly-	Lys-	Lys-	Arg-	Arg-	Pro-	Val-
	11	12	13	14	15	16	17	18	19	20
	Lys-	Val-	Try-	Pro-	Asp-	Gly-	Ala-	Glu-	Asp-	Gln-
	21	22	23	24	25	26	27	28	29	30
	Leu-	Ala-	Glu-	Ala-	Phe-	Pro-	Leu-	Glu-	Phe-	OH
	31	32	33	34	35	36	37	38	39	

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of H.P. Acthar Gel in the treatment of infantile spasms is unknown.

H.P. Acthar Gel and endogenous ACTH stimulate the adrenal cortex to secrete cortisol, corticosterone, aldosterone, and a number of weakly androgenic substances. Prolonged administration of large doses of H.P. Acthar Gel induces hyperplasia and hypertrophy of the adrenal cortex and continuous high output of cortisol, corticosterone and weak androgens. The release of endogenous ACTH is under the influence of the nervous system via the regulatory hormone released from the hypothalamus and by a negative corticosteroid feedback mechanism. Elevated plasma cortisol suppresses ACTH release.

H.P. Acthar Gel is also reported to bind to melanocortin receptors.

The trophic effects of endogenous ACTH and H.P. Acthar Gel on the adrenal cortex are not well understood beyond the fact that they appear to be mediated by cyclic AMP.

ACTH rapidly disappears from the circulation following its intravenous administration; in people, the plasma half-life is about 15 minutes. The pharmacokinetics of H.P. Acthar Gel have not been adequately characterized.

The maximal effects of a trophic hormone on a target organ are achieved when optimal amounts of hormone are acting continuously. Thus, a fixed dose of H.P. Acthar Gel will demonstrate a linear increase in adrenocortical secretion with increasing duration for the infusion.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Adequate and well-controlled studies have not been done in animals. Human use has not been associated with an increase in malignant disease [*see Warnings and Precautions (5.14) and Use in Specific Populations (8.1)*].

14 CLINICAL STUDIES

The effectiveness of H.P. Acthar Gel as a treatment for infantile spasms was demonstrated in a single blinded (video EEG interpreter blinded) clinical trial in which patients were randomized to receive either a 2 week course of treatment with H.P. Acthar Gel (75 U/m² intramuscular twice daily) or prednisone (1 mg/kg by mouth twice daily). The primary outcome was a comparison of the number of patients in each group who were treatment responders, defined as a patient having complete suppression of both clinical spasms and hypsarrhythmia on a full sleep cycle video EEG performed 2 weeks following treatment initiation, rated by an investigator blinded to treatment. Thirteen of 15 patients (86.7%) responded to H.P. Acthar Gel as compared to 4 of 14 patients (28.6%) given prednisone ($p<0.002$). The 2-week treatment was followed by a 2-week period of taper. Nonresponders to the prednisone treatment were eligible to receive H.P. Acthar Gel treatment. Seven of 8 patients (87.5%) responded to H.P. Acthar Gel after not responding to prednisone. Similarly, the 2 nonresponder patients from the H.P. Acthar Gel treatment were eligible to receive treatment with prednisone. One of the 2 patients (50%) responded to the prednisone treatment after not responding to H.P. Acthar Gel.

A supportive single-blind, randomized clinical trial comparing high-dose, long-duration treatment (150 U/m² once daily for 3 weeks, n=30) of H.P. Acthar Gel with low-dose, short-duration treatment (20 U once daily for 2 weeks, n=29) for the treatment of infantile spasms was also evaluated in infants and children less than 2 years of age. Nonresponders (defined as in the previously described study) in the low-dose group received a dose escalation at 2 weeks to 30 U once daily. Nominal statistical superiority of the high dose treatment, as compared to the low dose treatment, was observed for cessation of spasms but not for the resolution of hypsarrhythmia.

16 HOW SUPPLIED / STORAGE AND HANDLING

H.P. Acthar Gel (repository corticotropin injection) is supplied as 5 mL multi-dose vial (63004-8710-1) containing 80 USP Units per mL. H.P. Acthar Gel (repository corticotropin injection) should be warmed to room temperature before using. Do not over pressurize the vial prior to withdrawing the product.

Store H.P. Acthar Gel (repository corticotropin injection) under refrigeration between 2°-8°C (36°-46°F). Product is stable for the period indicated on the label when stored under the conditions described.

17 PATIENT COUNSELING INFORMATION

Caretakers of patients with infantile spasms should be informed of the availability of a Medication Guide, and they should be instructed to read the Medication Guide prior to administering H.P. Acthar Gel. Patients should be instructed to take H.P. Acthar Gel only as prescribed. They should not stop treatment suddenly unless instructed by their physician to do so.

Patients, their caregivers and families should be advised as to the importance of the need for careful monitoring while on and during titration from H.P. Acthar Gel treatment and the importance of not missing and scheduled doctor's appointments.

Patients, their caregivers and families should be advised that if the patient develops an infection or fever they should contact their physician. They should be educated that a fever may not necessarily be present during infection. The patient should also try to limit contact with other people with infections to minimize the risk of infection while taking H.P. Acthar Gel [*see Warnings and Precautions (5.1) and Adverse Reactions (6.1.1)*].

Patients, their caregivers and families should be advised that if the patient experiences an increase in blood pressure they should contact their physician [*see Warnings and Precautions (5.3) and Adverse Reactions (6.1.1)*].

Patients, their caregivers and families should be advised that if the patient or the caregiver notices blood or a change in color of the patient's stool they should contact their physician [*see Warnings and Precautions (5.6)*].

Caregivers and families of infants and children treated with H.P. Acthar Gel should be informed that the patient may show signs of irritability and sleep disturbances. These effects are reversible once H.P. Acthar Gel therapy is stopped [*see Warnings and Precautions (5.7) and Adverse Reactions (6.1.1)*].

Patients, their caregivers and families should be advised that changes in appetite, most often leading to weight gain, are seen with H.P. Acthar Gel therapy, becoming more frequent as the dose or treatment period increases. These effects are reversible once H.P. Acthar Gel therapy is stopped [*see Warnings and Precautions (5.12) and Adverse Reactions (6.1.1)*].

Patients, their caregivers and families should be advised that the patient may be monitored for signs of adrenal insufficiency such as weakness, fatigue, lethargy, anorexia, weight loss, hypotension, abdominal pain or hyperpigmentation (adults only) after treatment has stopped. Since the recovery of the adrenal gland varies from days to months, patients may need to be protected from the stress of trauma or surgery by the use of corticosteroids during the period of stress [*see Warnings and Precautions (5.2)*].

Patients should be advised not to be vaccinated with live or live attenuated vaccines during treatment with H.P. Acthar Gel. Additionally, other immunization procedures in patients or in family members who will be in contact with the patient should be undertaken with caution while the patient is taking H.P. Acthar Gel [*see Warnings and Precautions (5.4)*].

Patients, their caregivers and families should be advised that prolonged use of H.P. Acthar Gel in children may result in Cushing's syndrome and associated adverse reactions, may inhibit skeletal growth, and may cause osteoporosis and decreased bone density. If prolonged use is necessary, H.P. Acthar Gel should be given intermittently along with careful observation [*see Warnings and Precautions (5.2), (5.12), and (5.13) and Adverse Reactions (6.1.1)*].

Patients, their caregivers and families should be informed that H.P. Acthar Gel may mask symptoms of other diseases/disorders without altering the course of the other disease/disorder. The patient will need to be monitored carefully during and for a period following discontinuation of therapy for signs of infection, abnormal cardiac function, hypertension, hyperglycemia, change in body weight, and fecal blood loss [*see Warnings and Precautions (5.5)*].

In the treatment of Infantile Spasms, other types of seizures may occur because some patients with infantile spasms progress to other forms of seizures (for example, Lennox-Gastaut Syndrome). Additionally the spasms sometimes mask other seizures and once the spasms resolve after treatment with H.P. Acthar Gel, the other seizures may become visible. Parents and caregivers should inform their physician of any new onset of seizures so that appropriate management can then be instituted [*see Adverse Reactions (6.1.1)*].

H.P. Acthar® Gel
(repository corticotropin injection)

Manufactured for Questcor Pharmaceuticals, Inc.
Questcor Pharmaceuticals, Inc.
26118 Research Road
Hayward, CA 94545 USA

phone (800) 411-3065
(510) 400-0700

fax (510) 400-0799

PL065/Rev. 04 No. 1350
Issued: 09/2012 PM-459-02

QUESTCOR®

EXHIBIT F

A COMPARISON OF THE SAFETY/TOLERABILITY AND PHARMACODYNAMICS OF ACTHAR GEL AND METHYLPREDNISOLONE WITH REGIMENS UTILIZED FOR THE TREATMENT OF MS EXACERBATIONS

Stacie Bell, Jennifer Vincent, Vakessa Hammock, et al

Poster presented at the 2014 American Academy of Neurology Annual Meeting

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Stacie Bell, Jennifer Vincent, Vakessa H

INTRODUCTION

Acthar® Gel (Acthar) and intravenous methylprednisolone (IVMP) are both utilized to treat multiple sclerosis (MS) exacerbations. This study was conducted to evaluate the pharmacodynamics (PD) and safety profiles of subcutaneous Acthar and IVMP in healthy subjects, using dosage regimens of both drugs that have been commonly employed for treatment of MS exacerbations.

STUDY DESIGN & METHODS

Study Design

- Multiple-dose, randomized, open-label, crossover study
- 18 healthy male and female subjects (9 per treatment sequence)
- Key entry criteria:
  - –Ages of 18 and 50 years, inclusive
  - –BMI between 18.5 and 30 kg/m² at check-in
  - –HbA1c of ≥6.5% at screening
  - –No recent concomitant medication or glucocorticoid use (30 days–3 months)
- Dosing regimens: daily Acthar (80 U, SC) or daily IVMP (1 g over 30 min; Pfizer, New York) for 5 days
- 30-day washout between study periods with schedule repeated for Period 2
- Follow-up visits were completed for each study period

Study Metrics

- Cortisol response after Acthar and IVMP administration including:
  - –Cortisol exposure
  - –Total steroid exposure (based on cortisol equivalence) =
    AUEC cortisol + (MP AUC*Potency Factor of 5)
  - –Measured in both serum and plasma ultrafiltrate (PUF)
- Changes in total leukocyte (WBC) counts and WBC subpopulations
- Safety assessments:
  - –Adverse events (AEs)
  - –Physical exams
  - –Change from baseline laboratory results, ECGs, and vital signs

SUBJECT DISPOSITION & DEMOGRAPHICS

Subject Disposition

Enrolled	18	Completed	16
Early Discontinuation*	1	Lost to Follow-up	1

*Subject did not return for Period 2 due to scheduling issue.

Subject Demographics

Gender	Age Range	BMI Range	Race/Ethnicity
1:1 Male to Female	20–44	22.0–29.8	1:9 Non-Caucasian or Hispanic

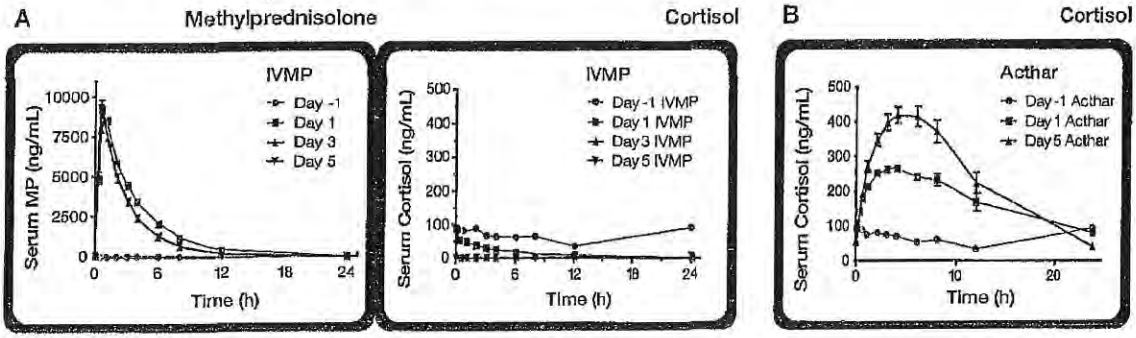
ARISON OF THE SAFETY/TOLERABILITY AND PHARMACODYNAMICS OF ACT
PREDNISOLONE WITH REGIMENS UTILIZED FOR THE TREATMENT OF MS EX

mmock, Karen Welch, Julia Chung, Mary Nyberg, Patrice Becker, and David Young.* Questc

RESULTS

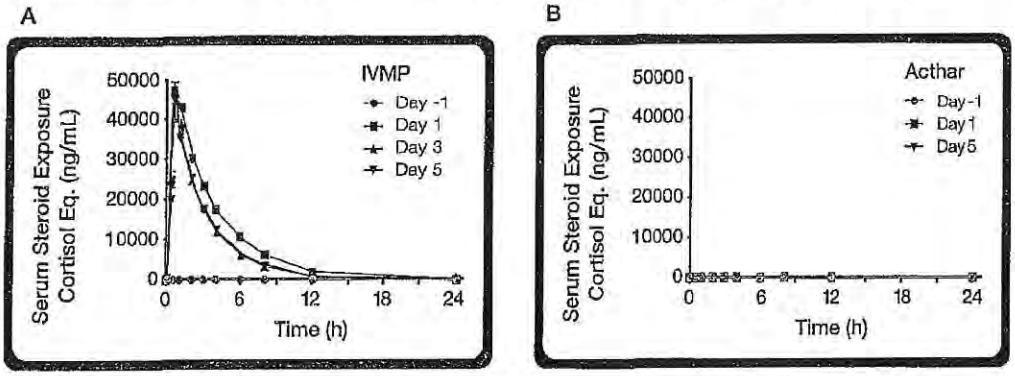
Steroidogenic Exposure Summary

Figure 1: Serum Methylprednisolone and Cortisol Exposure After IVMP or Acthar Administration



Panel A: MP and cortisol serum concentration-time profiles following IVMP administration.
Panel B: Cortisol serum concentration-time profile following Acthar administration.
Note: Difference in scale for cortisol. PUF profiles were similar with a lower concentration range (data not shown).
Mean ± SEM; N=17 for IVMP and N=18 for Acthar.

Figure 2: Total Steroid (Cortisol Equivalent) Exposure After IVMP or Acthar Administration



Panel A: Total steroid exposure (cortisol equivalent) concentration-time profiles following IVMP.
Panel B: Total steroid exposure (cortisol equivalent) concentration-time profiles following Acthar.
Mean ± SEM; N=17 for IVMP and N=18 for Acthar.

Table 1: Serum and Plasma Ultrafiltrate Exposure (Day 5)

Serum	Cortisol AUEC	MP AUC	Steroid Exposure AUEC	Serum (Total) Steroid Exposure	
IVMP	122	26012	134986	Acthar: IVMP ANOVA LSM	0.04 (0.01) p<0.001
Acthar	5432	—	5432		

PUF	Cortisol AUEC	MP AUC	Steroid Exposure AUEC	Plasma (Free) Steroid Exposure	
IVMP	7.57	656	3538	Acthar: IVMP ANOVA LSM	0.06 (0.03) p<0.001
Acthar	180	—	180		

AUEC comparison is based upon 80 U Acthar and 1 g IVMP daily for 5 days.
Steroid exposure is defined as cortisol equivalent AUEC. "PUF" is plasma ultrafiltrate.
AUC and AUEC units: hr*ng/mL; Acthar: IVMP exposure ratios are: Mean (SD).
ANOVA of least squares means